Palladium-Catalyzed Glycal Imidate Rearrangement: Formation of \( \alpha \)- and \( \beta \)-N-Glycosyl Trichloroacetamides

Jaemoon Yang, Gregory J. Mercer, and Hien M. Nguyen*

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717
hmnguyen@chemistry.montana.edu

Received July 25, 2007

ABSTRACT

A novel palladium(II)-catalyzed stereoselective synthesis of \( \alpha \)- and \( \beta \)-N-glycosyl trichloroacetamides has been developed. The \( \alpha \)- and \( \beta \)-selectivity at the anomeric carbon depends on the nature of the palladium–ligand catalyst. While the cationic palladium(II) promotes the \( \alpha \)-selectivity, the neutral palladium(II) favors the \( \beta \)-selectivity.

The stereoselective synthesis of \( \alpha \)- or \( \beta \)-N-glycosyl amides has recently received considerable attention since the recognition of glycoproteins is important in a variety of biochemical processes such as cell–cell recognition, cellular transport, adhesion for the binding of pathogens to cells, and metastasis. Early work on the synthesis of glycosyl amides employed the reaction of glycosyl amines with activated carboxylic acid derivatives. Although this method is still frequently used, drawbacks of this methodology include hydrolysis of the starting glycosyl amines as well as anomerization of the protected glycosyl azides upon reduction. In an alternative strategy, the glycosyl amides can be produced by treatment of isothiocyanates with the appropriate acids. In recent years, glycosyl amides have also been made via Staudinger reduction of glycosyl azides. Although this approach gives the desired glycosyl amides in good yields, the \( \alpha/\beta \)-selectivity at the anomeric carbon is poor. DeShong and several research groups, who recognized the challenge of this approach, developed a stereoselective synthesis of \( \alpha \)-N-glycosyl amides from glycosyl azides using isoxazoline intermediates. We report herein a novel method for the stereoselective synthesis of \( \alpha \)- and \( \beta \)-N-glycosyl amides involving Pd(II)-catalyzed glycal imidate rearrangement. In our approach, the nature of the palladium–ligand complex


controls the anomeric selectivity (Scheme 1). The cationic Pd(II), which promotes ionization of the glycal imidate 1 by coordinating to the imidate nitrogen, results in the formation of $\alpha$-N-glycosyl trichloroacetamide 2. In contrast, use of neutral Pd(II) promotes a concerted-type mechanism to provide $\beta$-N-glycosyl trichloroacetamide 3. Although the allylic imidate rearrangement is pioneered by Overman,9 there is no report on utilizing this method in carbohydrate synthesis to control the $\alpha$- and $\beta$-selectivity of the glycosyl amide at the anomeric carbon.

Treatment of glucal imidate 4 with 2.5 mol% of Pd(PhCN)$_2$Cl$_2$ in CH$_2$Cl$_2$ at 25 °C for 2 h provided a 1:1 mixture of $\alpha$- and $\beta$-N-glycosyl trichloroacetamide 5 in 60% yield (Table 1, entry 1). It was anticipated that the anomeric selectivity would depend on the ligand on palladium. Accordingly, glucal imidate 4 was treated with a preformed solution of Pd(PhCN)$_2$Cl$_2$ and P$_3$H$_3$, and 5 was isolated in 83% yield with $\alpha$: $\beta$ = 1:2 (entry 2). With the use of RUPHOS and DTTBP as the phosphine ligands,10 the anomeric selectivity was slightly improved, favoring the $\beta$-anomer (entries 3 and 4). Employing TTMPP as the phosphine ligand led to an improvement of both the yield and the $\beta$-selectivity (entry 5). However, it took 16 h for the reaction to go to completion. Gratifyingly, it was found that addition of 10 mol% of salicylaldehyde significantly shortened the reaction time to 4 h (entries 6 and 7), and the desired $\beta$-N-glycosyl trichloroacetamide 5 was obtained in good yield with excellent $\beta$-selectivity. Thus, the combination of the bulky phosphine ligand and salicylaldehyde increased both the yield and the $\beta$-selectivity as well as shortened the reaction time. We also examined whether temperature affected the selectivity; increasing or decreasing the reaction temperature only decreased the $\beta$-selectivity. This is the first example wherein a bulky phosphine ligand is employed to control the stereoselectivity at the anomeric carbon in the allylic imidate rearrangement.

### Table 1. Pd(II)-Catalyzed Formation of $\beta$-N-Glycosyl Trichloroacetamide

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphine</th>
<th>ligand</th>
<th>additive</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>$\alpha$: $\beta$</th>
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<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>none</td>
<td></td>
<td>2</td>
<td>60</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>P$_3$H$_3$</td>
<td>none</td>
<td></td>
<td>16</td>
<td>83</td>
<td>1:2</td>
</tr>
<tr>
<td>3</td>
<td>RUPHOS</td>
<td>none</td>
<td></td>
<td>16</td>
<td>77</td>
<td>1:3</td>
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<tr>
<td>4</td>
<td>DTTBP</td>
<td>none</td>
<td></td>
<td>25</td>
<td>73</td>
<td>1:4</td>
</tr>
<tr>
<td>5</td>
<td>TTMPP</td>
<td>none</td>
<td></td>
<td>16</td>
<td>89</td>
<td>1:7</td>
</tr>
<tr>
<td>6</td>
<td>DTTBP</td>
<td>10 mol% of salicylaldehyde</td>
<td></td>
<td>4</td>
<td>70</td>
<td>1:7</td>
</tr>
<tr>
<td>7</td>
<td>TTMPP</td>
<td>10 mol% of salicylaldehyde</td>
<td></td>
<td>4</td>
<td>86</td>
<td>1:9</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>10 mol% of salicylaldehyde</td>
<td></td>
<td>1</td>
<td>71</td>
<td>1:2</td>
</tr>
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*All reactions were carried out in CH$_2$Cl$_2$ (0.2 M) with 2.5 mol% of Pd(II)/phosphine ligand. $^b$Isolated yield. $^c$$^1$H NMR ratio.

When cationic palladium,11 Pd(TH$_2$CN)$_2$(BF$_4$)$_2$, was employed in the reaction, the desired $\alpha$-N-glycosyl trichloroacetamide 5 was obtained in 73% yield as the major anomer (Table 2, entry 1). Addition of 10 mol% of salicylaldehyde significantly increased the $\alpha$-selectivity (entry 2).12 Decreasing the catalyst loading still maintained the yield and the selectivity (entries 3 and 4). Thus, switching to the cationic palladium reverses the anomeric selectivity, favoring the $\alpha$-anomer.13

### Table 2. Pd(II)-Catalyzed Formation of $\alpha$-N-Glycosyl Trichloroacetamide

<table>
<thead>
<tr>
<th>entry</th>
<th>palladium</th>
<th>salicylaldehyde</th>
<th>time (min)</th>
<th>yield (%)</th>
<th>$\alpha$: $\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 mol%</td>
<td>none</td>
<td>45</td>
<td>73</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>2.5 mol%</td>
<td>10 mol%</td>
<td>1</td>
<td>80</td>
<td>14:1</td>
</tr>
<tr>
<td>3</td>
<td>0.1 mol%</td>
<td>0.4 mol%</td>
<td>2</td>
<td>78</td>
<td>9:1</td>
</tr>
<tr>
<td>4</td>
<td>0.5 mol%</td>
<td>2 mol%</td>
<td>1</td>
<td>82</td>
<td>13:1</td>
</tr>
</tbody>
</table>

*All reactions were carried out in CH$_2$Cl$_2$ with Pd(TH$_2$CN)$_2$(BF$_4$)$_2$ and salicylaldehyde (1:4) except for entry 1. $^b$Isolated yield. $^c$$^1$H NMR ratio.

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To assess the feasibility of this palladium reaction for the synthesis of \( \beta \)-\( N \)-glycosyl trichloroacetamides, glycal imidates incorporating cyclic ketal protecting groups were investigated (Figure 1). The desired products 6–10 were obtained with good \( \beta \)-selectivity. The deactivating effect of 4,6-acetal protecting groups on these glycal imidates restricts them in the \( \text{tag} \) conformations, thus limiting ionization to favor \( \beta \)-anomers. In contrast, glycal imidates incorporating acyclic protecting groups gave a mixture of \( \alpha \)- and \( \beta \)-\( N \)-glycosyl trichloroacetamides such as 11 and 12.

In the formation of \( \alpha \)-\( N \)-glycosyl trichloroacetamides, a number of glycal imidates incorporating a variety of cyclic and acyclic protecting groups were examined (Figure 2). The desired glycosyl amides 6–13 were obtained with excellent \( \alpha \)-selectivity. These results suggest that the cationic palladium–salicylaldehyde complex was responsible for the observed \( \alpha \)-selectivity at the anomeric center and the protecting groups on the glycal imidates had little effect on the selectivity.

The proposed mechanism for Pd(II)-catalyzed formation of \( \alpha \)- and \( \beta \)-\( N \)-glycosyl trichloroacetamides is outlined in Figure 3. In the case of the cationic palladium, the Pd(CH\( \text{CN} \))\textsubscript{2}Cl\textsubscript{2}–salicylaldehyde complex coordinates to the imidate nitrogen of 4 to form \( \pi \)-complex 16, which is activated toward nucleophilic attack by the imidate nitrogen. Subsequent cyclization of 16 provides \( \sigma \)-complex 17. Grob-like fragmentation followed by dissociation releases \( \beta \)-anomer 5.

The glycosyl urea is found in nature as a structural unit of glycoscinamoyl spermidine antibiotics. There are several methods reported for the construction of glycosyl urea. To demonstrate the utility of the 2,3-unsaturated glycosyl

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(13) We also investigated whether the glycal imidate rearrangement could be catalyzed by a Lewis acid. Accordingly, treatment of 4 with 0.5 mol % of TMSOTf in CH\(_2\)Cl\(_2\) at 0 °C only resulted in decomposition.


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![Figure 1](image1.png)

**Figure 1.** Stereospecific formation of \( \beta \)-\( N \)-glycosyl trichloroacetamides. All reactions were performed with 2.5 mol % of Pd(Ph\( \text{CN} \))\textsubscript{2}Cl\textsubscript{2}/TTMPP and 10 mol % of salicylaldehyde. \( b \) Isolated yield. \( c \) \( ^1\text{H} \) NMR ratio.

![Figure 2](image2.png)

**Figure 2.** Stereospecific formation of \( \alpha \)-\( N \)-glycosyl trichloroacetamides. All reactions were performed with 0.5 mol % of Pd(CH\( \text{CN} \))\textsubscript{2}(BF\(_4\))\textsubscript{2} and 2 mol % of salicylaldehyde. \( b \) Isolated yield. \( c \) \( ^1\text{H} \) NMR ratio.

![Figure 3](image3.png)

**Figure 3.** Proposed mechanism for the \( \alpha \)-/\( \beta \)-selectivity.
amide products, both the α- and β-N-glycosyl trichloroacetamides were transformed into the corresponding glycosyl ureas 18–23 by dihydroxylation of N-glycosyl trichloroacetamides and subsequent treatment with Cs$_2$CO$_3$ and amines in DMF (Scheme 2). The diol and triol intermediates of certain glycosyl ureas were acylated to ease the purification process.

In summary, a novel method for palladium(II)-catalyzed stereoselective formation of α- and β-N-glycosyl trichloroacetamides has been developed. The α- and β-selectivity at the anomeric carbon depends on the nature of the palladium–ligand catalyst. While the cationic palladium–salicylaldehyde complex promotes the α-selectivity, the neutral palladium–ligand catalyst favors the β-selectivity. Because of its substrate tolerance and mild conditions, this palladium method is applicable to a wide range of glycal imidates. The resulting N-glycosyl trichloroacetamides were further transformed into glycosyl ureas.

Acknowledgment. We thank Montana State University and NSF EPSCoR for financial support.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.
